JAMA | Review

Hypercalcemia
A Review

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IMPORTANCE Hypercalcemia affects approximately 1% of the worldwide population. Mild hypercalcemia, defined as total calcium of less than 12 mg/dL (<3 mmol/L) or ionized calcium of 5.6 to 8.0 mg/dL (1.4-2 mmol/L), is usually asymptomatic but may be associated with constitutional symptoms such as fatigue and constipation in approximately 20% of people. Hypercalcemia that is severe, defined as total calcium of 14 mg/dL or greater (>3.5 mmol/L) or ionized calcium of 10 mg/dL or greater (≥2.5 mmol/L) or that develops rapidly over days to weeks, can cause nausea, vomiting, dehydration, confusion, somnolence, and coma.

OBSERVATIONS Approximately 90% of people with hypercalcemia have primary hyperparathyroidism (PHPT) or malignancy. Additional causes of hypercalcemia include granulomatous disease such as sarcoidosis, endocrinopathies such as thyroid disease, immobilization, genetic disorders, and medications such as thiazide diuretics and supplements such as calcium, vitamin D, or vitamin A. Hypercalcemia has been associated with sodium-glucose cotransporter 2 protein inhibitors, immune checkpoint inhibitors, denosumab discontinuation, SARS-CoV-2, ketogenic diets, and extreme exercise, but these account for less than 1% of causes. Serum intact parathyroid hormone (PTH), the most important initial test to evaluate hypercalcemia, distinguishes PTH-dependent from PTH-independent causes. In a patient with hypercalcemia, an elevated or normal PTH concentration is consistent with PHPT, while a suppressed PTH level (<20 pg/mL depending on assay) indicates another cause. Mild hypercalcemia usually does not need acute intervention. If due to PHPT, parathyroidectomy may be considered depending on age, serum calcium level, and kidney or skeletal involvement. In patients older than 50 years with serum calcium levels less than 1 mg above the upper normal limit and no evidence of skeletal or kidney disease, observation may be appropriate. Initial therapy of symptomatic or severe hypercalcemia consists of hydration and intravenous bisphosphonates, such as zoledronic acid or pamidronate. In patients with kidney failure, denosumab and dialysis may be indicated. Glucocorticoids may be used as primary treatment when hypercalcemia is due to excessive intestinal calcium absorption (vitamin D intoxication, granulomatous disorders, some lymphomas). Treatment reduces serum calcium and improves symptoms, at least transiently. The underlying cause of hypercalcemia should be identified and treated. The prognosis for asymptomatic PHPT is excellent with either medical or surgical management. Hypercalcemia of malignancy is associated with poor survival.

CONCLUSIONS AND RELEVANCE Mild hypercalcemia is typically asymptomatic, while severe hypercalcemia is associated with nausea, vomiting, dehydration, confusion, somnolence, and coma. Asymptomatic hypercalcemia due to primary hyperparathyroidism is managed with parathyroidectomy or observation with monitoring, while severe hypercalcemia is typically treated with hydration and intravenous bisphosphonates.

Multimedia

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Hypercalcemia is defined by a serum calcium value above the upper limit of the normal range, defined as greater than 2 SDs above the population mean.[1] Hypercalcemia affects approximately 1% of the general population and approximately 2% of patients with cancer.[2-4] The annual incidence of hypercalcemia is 0.09% to 0.6%, varying by population screened.[5,6] Approximately 90% of people with hypercalcemia have primary hyperparathyroidism (PHPT) or malignancy. However, hypercalcemia may be due to any of a large number of disorders. Optimal management requires identifying the etiology of hypercalcemia. This Review summarizes the pathophysiology, diagnosis, and treatment of hypercalcemia.

Methods

A search of PubMed was conducted on February 23, 2022, and updated on April 20, 2022, and July 12, 2022, using the key word *hypercalcemia*. The search was restricted to English-language articles published within the past 10 years. We also searched with key words *hypercalcemia* and *epidemiology*, *diagnosis*, *treatment*, *incidence*, *survival*, and *mortality* without year restriction. Of 7533 identified articles, 98 were included, consisting of 13 randomized clinical trials (RCTs), 4 meta-analyses, 17 longitudinal studies, 14 cross-sectional studies, 29 case reports/case series, and 21 reviews.

Observations and Discussion

Normal Regulation of Calcium

Calcium is essential in skeletal mineralization, intracellular signaling, nerve conduction, muscle contraction, hormone secretion, and other biological processes. Approximately 50% of total calcium is ionized and biologically active. The remainder is bound to albumin and immunoglobulins in a pH-dependent manner (40%-45%) or complexed with anions (approximately 10%). In adults, normal serum total and ionized calcium concentrations are 8.5 to 10.5 mg/dL (2.12-2.62 mmol/L) and 4.8 to 5.6 mg/dL (1.20-1.40 mmol/L), respectively, with reference ranges varying by laboratory.

Parathyroid hormone (PTH) and vitamin D regulate skeletal mobilization, kidney excretion, and intestinal absorption of calcium to achieve calcium homeostasis. Because of its physiological importance, serum ionized calcium is tightly regulated.[7] A calcium-sensing receptor (CaSR), highly expressed on parathyroid cells, detects changes in ionized calcium. A decrease in ionized calcium activates the CaSR and triggers a rapid release of PTH within minutes,[8,9] which restores serum ionized calcium toward baseline. Parathyroid hormone stimulates osteoclast-mediated bone resorption, releasing skeletal calcium into the serum.[10] Parathyroid hormone facilitates calcium reabsorption in the distal nephron by increasing the activity and/or expression of cation channels, calcium-shuttling proteins, and basolateral membrane exchangers[11] and in the loop of Henle by stimulating paracellular calcium reabsorption.[12] In the proximal nephron, PTH increases 1α-hydroxylase (CYP27B1) transcription, which stimulates conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol). This results in calcitriol-mediated upregulation of calcium channels and exchangers in the small intestine, increasing absorption.[13]

Etiology and Pathophysiology of Hypercalcemia

Hypercalcemia develops when calcium entry into the serum exceeds skeletal deposition and/or kidney excretion. Rapidly developing or moderately severe hypercalcemia causes kidney-afferent arterial vasoconstriction, reduced glomerular filtration rate, and impaired kidney function. Hypercalcemia also causes nephrogenic diabetes insipidus by downregulating aquaporin and impairing osmotic gradient generation. This exacerbates volume contraction and reduces glomerular filtration rate, worsening hypercalcemia. Thus, moderate to severe hypercalcemia, once established, initiates a self-perpetuating cycle.

The pathophysiology of hypercalcemia varies by etiology (**Box 1**). Increased bone resorption, reduced kidney calcium clearance, increased gastrointestinal calcium absorption, or a combination may contribute. Approximately 90% of patients with hypercalcemia have PHPT or hypercalcemia of malignancy.

In PHPT, excess PTH, typically secreted by a single benign parathyroid adenoma, acts directly or indirectly on its target organs, bone, kidney, and the gastrointestinal tract. Parathyroid hormone stimulates bone resorption and conversion of calcidiol to calcitriol, which increases gastrointestinal calcium absorption. Although filtered glomerular calcium consequently increases, PTH enhances kidney calcium reabsorption, exacerbating hypercalcemia.[14] Mechanisms underlying hypercalcemia vary by cancer type. In humoral hypercalcemia of malignancy, tumors secrete parathyroid hormone–related protein (PTHrP), a protein with homology to PTH, which binds to and activates the PTH1 receptor. Similar to PHPT, PTHrP-induced hypercalcemia involves increased bone resorption and kidney calcium reabsorption. In contrast, skeletal metastases and myeloma cause hypercalcemia via focal increases in osteoclastic bone resorption (osteolysis) mediated by local paracrine factors (interleukins, receptor activator of nuclear factor–κB ligand, PTHrP, etc) produced by tumor or neighboring cells in the bone microenvironment.[15] In some hematologic malignancies and lymphomas, hypercalcemia is caused by ectopic overproduction of calcitriol from macrophage 1α-hydroxylase activity induced by malignant cells, which, unlike proximal kidney tubule cells, are unresponsive to feedback.[16]

Milk-alkali syndrome from excess calcium carbonate ingestion results from increased intestinal absorption and reduced kidney excretion of calcium.[17,18] Thiazides can cause PTH-independent hypercalcemia by promoting increased kidney calcium reabsorption. Many patients, however, continue to have hypercalcemia after thiazide discontinuation, indicating underlying PHPT.[19] Both noninfectious and infectious granulomatous diseases may cause calcitriol-mediated hypercalcemia. Sarcoidosis and tuberculosis most commonly cause dysregulated CYP27B1 production by macrophages, which in turn increases calcitriol-mediated intestinal calcium absorption. Increased bone resorption also contributes to hypercalcemia.

Recently Reported Associations

Several medications and conditions have recently been associated with hypercalcemia. Case reports have documented reversible hypercalcemia with sodium-glucose cotransporter protein 2 inhibitors, likely due to osmotic diuresis and volume contraction. Underlying risk factors (dehydration, high calcium intake, thiazides, acidosis, undiagnosed PHPT) were typically present.[20] Estimates of the frequency are not available, but a meta-analysis of 25 RCTs indicated that the increase in serum calcium was not consistent with a meaningful

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Box 1. Causes of Hypercalcemia

I. Increased bone resorption
- A. Parathyroid hormone mediated
  1. Sporadic primary hyperparathyroidism
  2. Familial/inherited primary hyperparathyroidism
     - a. Multiple endocrine neoplasia
     - b. Familial isolated hyperparathyroidism
     - c. Hyperparathyroidism jaw-tumor syndrome
     - d. Familial hypocalciuric hypercalcemia (*CASR*, *GNA11*, *AP2S1* variants, etc)
     - e. Neonatal severe hyperparathyroidism (*CASR* variant)
  3. Parathyroid cancer
  4. Tertiary hyperparathyroidism
  5. Drugs—lithium
  6. Malignancy—ectopic parathyroid hormone production (rare)
- B. Non–parathyroid hormone mediated
  1. Malignancy
     - a. Humoral hypercalcemia of malignancy (parathyroid hormone–related protein)
     - b. Osteolytic metastases or myeloma
  2. Immobilization
  3. Vitamin A toxicity
  4. Hyperthyroidism
  5. Drugs—teriparatide, abaloparatide, rebound after denosumab discontinuation
  6. Jansen-type metaphyseal chondrodysplasia (activating *PTH1R* variant)
  7. Humoral hypercalcemia of benignancy (parathyroid hormone–related protein secretion by benign tissue)

II. Increased gastrointestinal absorption
- A. Vitamin D mediated
  1. Hypervitaminosis D
  2. 1,25-dihydroxyvitamin D mediated
     - a. Hematologic malignancies (increased 1α-hydroxylase activity)
     - b. Granulomatous disorders
       - i. Infectious—tuberculosis, cat-scratch disease, histoplasmosis, cryptococcosis, candidiasis, leprosy, *Pneumocystis jirovecii*, etc
       - ii. Inflammatory—sarcoid, Wegener granulomatosis, Crohn disease, Blau syndrome, Langerhans cell histiocytosis, etc
       - iii. Foreign body—silicosis, talc, bacille Calmette-Guérin therapy, berylliosis, paraffin oil
       - iv. Other—subcutaneous fat necrosis of the newborn, lipoid pneumonia
     - c. Drugs—calcitriol, activated vitamin D analog ingestion, 8-chloro-cyclic adenosine monophosphate
     - d. Congenital—*CYP24A1* variant, *SLC34A1* variant
- B. Non–vitamin D mediated
  1. Lactase deficiency
  2. Sucrase-isomaltase deficiency

III. Reduced kidney clearance
- A. Drugs—thiazides
- B. Milk-alkali syndrome (concomitant with excess calcium carbonate ingestion)
- C. Acute kidney failure
- D. Bartter syndrome
- E. Adrenal insufficiency

IV. Other or unclear mechanism
- A. Reduced deposition of skeletal calcium
  1. Adynamic bone disease
  2. Hypophosphatasia
- B. Redistribution—rhabdomyolysis
- C. Other or unknown—acromegaly, pheochromocytoma, theophylline, ketogenic diet, kidney tubular acidosis, foscarnet, omeprazole, aromatase inhibitors, sodium-glucose cotransporter 2 protein inhibitors, immune checkpoint inhibitors, calcium-sulfate beads, COVID-19, Williams syndrome

change.[21] Hypercalcemia has been reported infrequently with immune checkpoint inhibitors (ICIs).[22] In an RCT of patients with recurrent squamous cell carcinoma, hypercalcemia occurred in 1.3% treated with nivolumab vs 0.9% treated with standard therapy.[23] A case series of patients receiving ipilimumab therapy in clinical trials reported that 2 of 256 (0.8%) developed hypercalcemia.[24] Mechanisms may include ICI-induced endocrine disorders (hyperthyroidism, adrenal insufficiency), sarcoid-like granuloma formation, ICI-related PTHrP production, the malignancy itself, or transient ICI-related "hyperprogression" of disease.[25-28] Denosumab, a human monoclonal antibody, prevents receptor activator of nuclear factor-κB ligand interaction with its receptor, thereby inhibiting osteoclastogenesis. Hypercalcemia may occur after denosumab discontinuation due to "rebound" osteoclastic bone resorption. Most cases involve children younger than 18 years and those using denosumab for bone tumors and fibrous dysplasia.[29] A few cases have been reported in adults treated for osteoporosis. Transient hypercalcemia has been reported following use of antibiotic-eluting absorbable calcium sulfate beads during orthopedic procedures.[30,31]

The incidence of hypercalcemia in hospitalized patients with COVID-19 is rare (exact frequency unknown), but it is associated with poorer prognosis.[32] Potential mechanisms include rhabdomyolysis, immobilization, and post–COVID-19 granulomatous disease.[32-36] Fourteen children with epilepsy who were following a ketogenic diet were reported to develop hypercalcemia.[37] The mechanism, while not fully delineated, may be due to low bone formation.[37] Hypercalcemia has been described after after hours of intense exercise (frequency of approximately 18%); bone-resorptive markers increased and correlated with changes in calcium and vasopressin levels.[38]

Clinical Presentation

The symptoms and signs of hypercalcemia are determined by the severity of hypercalcemia and the rate of increase in serum calcium (**Box 2**). The presence of symptoms of hypercalcemia suggests a more severe and rapidly progressive condition, like malignancy. In contrast, asymptomatic hypercalcemia that is mild, chronic, and discovered incidentally is more likely due to PHPT. There is no universally accepted classification of mild, moderate, or severe hypercalcemia. One widely used classification defines mild hypercalcemia as total calcium of less than 12 mg/dL (<3 mmol/L) or ionized calcium of 5.6 to 8.0 mg/dL (1.4-2 mmol/L); moderate hypercalcemia as total calcium of 12 to 13.9 mg/dL (3-3.5 mmol/L) or ionized calcium of 10 mg/dL or greater (≥2.5 mmol/L); and severe hypercalcemia as 14 mg/dL or greater (≥3.5 mmol/L) or ionized calcium of 10 to 12 mg/dL (2.5-3 mmol/L).[39]

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Mild hypercalcemia is typically asymptomatic or characterized by nonspecific constitutional symptoms, such as fatigue and constipation. Even moderate hypercalcemia may be well tolerated if it is chronic or has a slow onset (over months). In contrast, large or abrupt increases in serum calcium (over days to weeks) usually cause multisystemic symptoms, such as fatigue, anorexia, polyuria, and polydipsia. Such elevations in ionized calcium concentrations cause hyperpolarization of neuromuscular cell membranes, which may become refractory to stimulation. Neuropsychiatric symptoms (ie, hyporeflexia, lethargy, altered mental status), slowed peristalsis causing gastrointestinal symptoms (ie, nausea, vomiting, and constipation), musculoskeletal symptoms (such as muscle weakness), and cardiovascular sequelae (such as prolonged PR interval, short QT interval, arrhythmias) can result (Box 2). Hypercalciuria causes polyuria and volume depletion, resulting in polydipsia. Severe hypercalcemia may cause confusion, stupor, and even coma.

Box 2. Clinical Presentation of Moderate to Severe Acute Hypercalcemia

Constitutional
Fatigue
Muscle weakness

Kidney
Nephrogenic diabetes insipidus
Polyuria
Polydipsia
Dehydration
Kidney insufficiency (acute or chronic)

Gastrointestinal
Anorexia
Nausea, vomiting
Constipation
Pancreatitis

Neurological
Hyporeflexia
Decreased ability to concentrate
Lethargy
Confusion
Stupor
Coma

Cardiovascular
Prolonged PR interval
Short QT interval
Widened QRS complex
Arrhythmia (usually bradycardia)

Assessment and Diagnosis

General Considerations

The etiology of hypercalcemia may be suggested by duration (acute vs chronic), presentation (symptomatic vs asymptomatic), and severity, as well as a patient's history (known metastatic cancer, vitamin D supplements). Therefore, the history should focus on these aspects, as well as family history and medication and supplement use. Physical examination findings are typically normal in mild hypercalcemia. Severe hypercalcemia is characterized by signs of dehydration. Occasionally, physical examination findings, such as lymphadenopathy, may suggest a particular cause of hypercalcemia (**Figure 1**).

The first step in the laboratory evaluation is to confirm hypercalcemia. Total calcium levels may not accurately reflect ionized calcium levels. Low albumin levels may mask hypercalcemia, while high albumin may result in "pseudo-hypercalcemia." Algorithms to adjust for albumin level are widely used but accuracy may be poor (in the presence of kidney disease, acid-base disorders, or anion perturbations).[40-42] In these situations, measurement of ionized calcium may be preferred, if available. In most outpatients with mild or moderate hypercalcemia that is asymptomatic (Figure 1), serum PTH should be measured first. However, in those with severe or symptomatic hypercalcemia without obvious cause, additional tests (vitamin D metabolites, tumor markers, electrophoresis, imaging, etc) should be obtained along with serum PTH, guided by clinical judgment based on the history, examination, or other available data.

PTH-Dependent Hypercalcemia

It is useful to classify hypercalcemia as PTH-dependent or PTH-independent to distinguish between PHPT and malignancy. Therefore, serum PTH level is the most useful initial test. The sensitivity of second-generation intact and third-generation "whole" PTH 2-site immunometric assays is similar and is approximately 90%.[43] In PHPT, the most common cause of hypercalcemia among patients in the ambulatory setting, PTH levels are elevated in approximately 80% of patients, although temporal trends suggest lower levels compared with past decades.[44,45] Because serum PTH should be suppressed in the setting of hypercalcemia, levels within the normal range are inappropriate and consistent with PHPT. In a study assessing the utility of intact PTH to discriminate PHPT from hypercalcemia of malignancy, all patients (n = 37) with hypercalcemia of malignancy had PTH levels of less than 20 pg/mL (normal range, 15-65 pg/mL).[46] Familial hypocalciuric hypercalcemia (FHH), most often caused by a heterozygous *CASR* inactivating variant, should also be considered if PTH is normal because 80% of patients with FHH have such a profile.[47]

PTH-Independent Hypercalcemia

Malignancy, the other main cause of hypercalcemia and the most common cause in hospitalized patients, should be considered when PTH levels are suppressed, with the precise evaluation tailored to clinical suspicion. An elevated PTHrP usually indicates hypercalcemia of malignancy, but measurement may be unnecessary because most patients with hypercalcemia of malignancy have advanced, previously diagnosed malignancies. Rarely, ectopic PTH secreted by certain malignant tumors may cause hypercalcemia of malignancy.

Elevated serum 25-hydroxyvitamin D concentrations suggest vitamin D intoxication. Patients with vitamin D intoxication typically have levels above 100 to 150 ng/mL (250-374 nmol/L). The minimum level required to cause hypercalcemia is uncertain. The presence of an underlying hypercalcemic disorder (eg, PHPT) or use of certain medications such as thiazides or lithium may lower the threshold.[48] Although an intake of 4000 IU/d of vitamin D has been considered the highest dose that is safe, a recent meta-analysis

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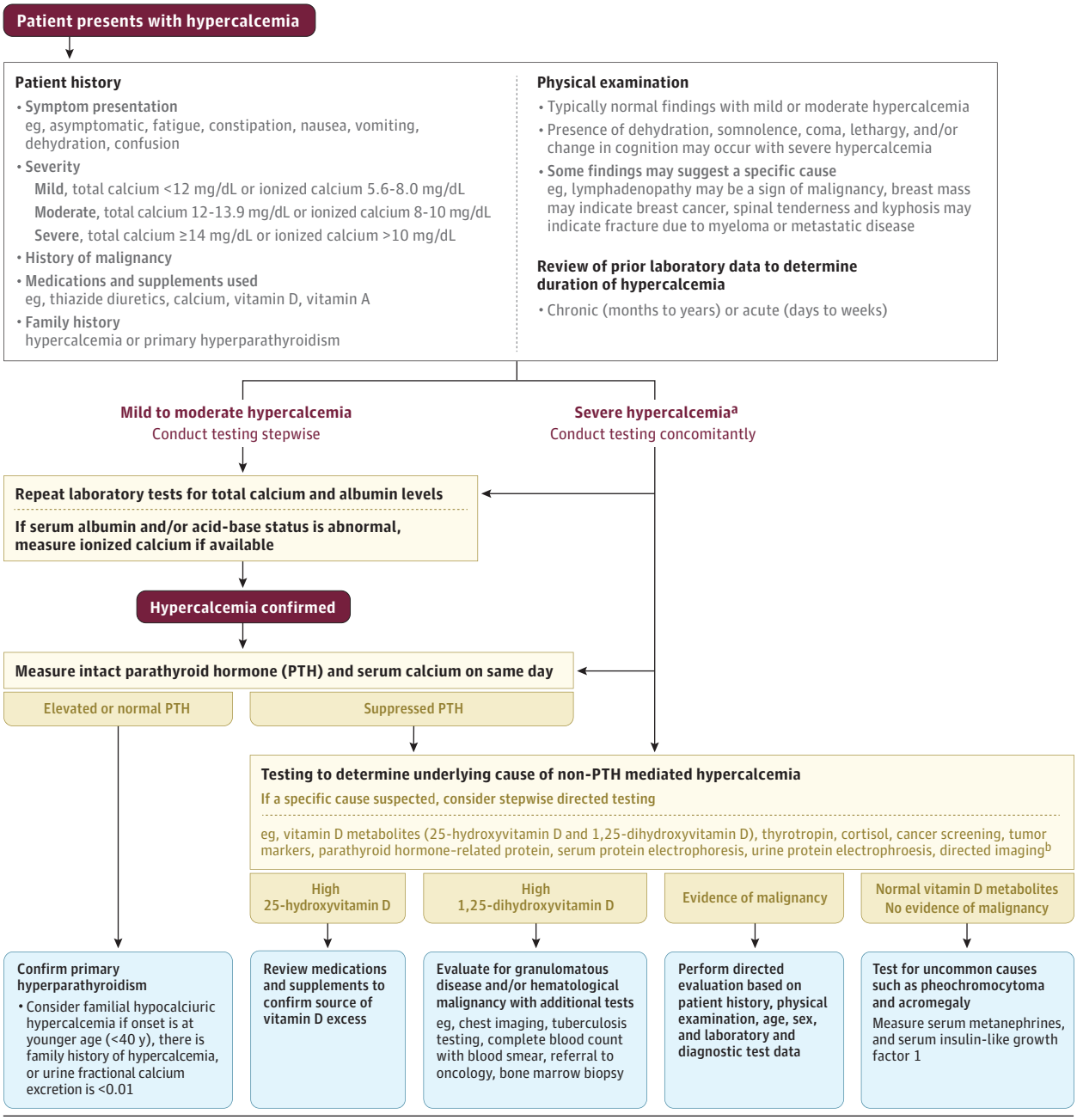
Figure 1. Approach to Diagnosis of Hypercalcemia


Patient presents with hypercalcemia
Patient history
• Symptom presentation
eg, asymptomatic, fatigue, constipation, nausea, vomiting, dehydration, confusion
• Severity
Mild, total calcium <12 mg/dL or ionized calcium 5.6-8.0 mg/dL
Moderate, total calcium 12-13.9 mg/dL or ionized calcium 8-10 mg/dL
Severe, total calcium ≥14 mg/dL or ionized calcium >10 mg/dL
• History of malignancy
• Medications and supplements used
eg, thiazide diuretics, calcium, vitamin D, vitamin A
• Family history
hypercalcemia or primary hyperparathyroidism
Physical examination
• Typically normal findings with mild or moderate hypercalcemia
• Presence of dehydration, somnolence, coma, lethargy, and/or change in cognition may occur with severe hypercalcemia
• Some findings may suggest a specific cause
eg, lymphadenopathy may be a sign of malignancy, breast mass may indicate breast cancer, spinal tenderness and kyphosis may indicate fracture due to myeloma or metastatic disease
Review of prior laboratory data to determine duration of hypercalcemia
• Chronic (months to years) or acute (days to weeks)
Mild to moderate hypercalcemia
Conduct testing stepwise
Severe hypercalcemia[a]
Conduct testing concomitantly
Repeat laboratory tests for total calcium and albumin levels
If serum albumin and/or acid-base status is abnormal, measure ionized calcium if available
Hypercalcemia confirmed
Measure intact parathyroid hormone (PTH) and serum calcium on same day
Elevated or normal PTH
Suppressed PTH
Testing to determine underlying cause of non-PTH mediated hypercalcemia
If a specific cause suspected, consider stepwise directed testing
eg, vitamin D metabolites (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D), thyrotropin, cortisol, cancer screening, tumor markers, parathyroid hormone–related protein, serum protein electrophoresis, urine protein electrophroesis, directed imaging[b]
High 25-hydroxyvitamin D
High 1,25-dihydroxyvitamin D
Evidence of malignancy
Normal vitamin D metabolites No evidence of malignancy
Confirm primary hyperparathyroidism
• Consider familial hypocalciuric hypercalcemia if onset is at younger age (<40 y), there is family history of hypercalcemia, or urine fractional calcium excretion is <0.01
Review medications and supplements to confirm source of vitamin D excess
Evaluate for granulomatous disease and/or hematological malignancy with additional tests
eg, chest imaging, tuberculosis testing, complete blood count with blood smear, referral to oncology, bone marrow biopsy
Perform directed evaluation based on patient history, physical examination, age, sex, and laboratory and diagnostic test data
Test for uncommon causes such as pheochromocytoma and acromegaly
Measure serum metanephrines, and serum insulin-like growth factor 1

This diagnostic algorithm has not been validated previously.

[a] In patients with severe hypercalcemia, a stepwise diagnostic approach is not recommended. Laboratory tests should be ordered simultaneously to confirm hypercalcemia, measure intact PTH, and assess for common causes of non–PTH-mediated hypercalcemia (eg, vitamin D metabolites). Treatment should be initiated while awaiting results.

[b] Imaging based on history, physical examination, and laboratory tests, eg, mammogram, chest x-ray.

of 48 studies with 19 833 participants demonstrated that mean daily vitamin D doses of 2354 IU were associated with a 50% (risk ratio, 1.54) increase in risk of hypercalcemia.[49,50]

Elevated serum calcitriol concentrations suggest excess intake, ectopic production, or, more rarely, genetic variants in the vitamin D metabolic pathway (Box 1). A case series of 101 patients indicated that sarcoidosis was the most common cause of calcitriol-mediated hypercalcemia (49%), followed by hematologic malignancy (17%) and infections (8%).[51] Chest imaging may help detect lymphadenopathy associated with sarcoidosis or hematologic malignancy.

Other Testing

Suppressed PTH with normal PTHrP and vitamin D levels suggest other causes (Box 1), such as medications (thiazides, vitamin A, thyroxine, PTH analogs), osteolytic metastases, myeloma, immobilization, hyperthyroidism, or other less common conditions. Thyroid function tests,

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Table 1. Typical Biochemical Profile, Pathophysiology, and Treatment of Various Etiologies of Hypercalcemia

Condition	Relative frequency[52]	Pathophysiology	Laboratory tests				Specific treatment
			Calcium	PTH	Phosphorus	Urine calcium	
Primary hyperparathyroidism[a]	54%	Excess PTH increases bone resorption, kidney calcium reabsorption, calcitriol production, gastrointestinal absorption	Usually mild elevation[b]	High or normal	Normal or low	Normal or high	Parathyroidectomy or observation; cinacalcet can be used for severe chronic hypercalcemia in patients who are not surgical candidates
Malignancy	35%						
Humoral hypercalcemia of malignancy		Tumors secrete parathyroid hormone–related protein, which has actions similar to PTH	Moderate to severe elevation	Low	Normal or low	Normal or high	Control underlying malignancy to extent possible; hydration; bisphosphonates; denosumab
Osteolytic metastases		Tumors cause focal increases in bone resorption	Moderate to severe elevation	Low	Normal or high	Normal or high	Zoledronic acid and denosumab
Calcitriol-producing lymphomas		Ectopic 1,25-dihydroxyvitamin D production increases gastrointestinal calcium absorption and bone resorption	Moderate to severe elevation	Low	High	Normal or high	Treat underlying malignancy; steroids
All other causes	11%						
Familial hypocalciuric hypercalcemia		Variants in calcium-sensing receptor increase set point for serum calcium	Mild elevation	Normal or high normal	Normal or low	Low	No treatment typically required
Vitamin D intoxication[c]		Increased gastrointestinal calcium absorption	Elevated	Low	High	Normal or high	Discontinue vitamin D ingestion; steroids if severe or recurrent hypercalcemia
Sarcoid[d]		Ectopic 1,25-dihydroxyvitamin D production increases gastrointestinal calcium absorption, and bone resorption	Elevated	Low	High	Normal or high	Steroids; limit dietary calcium and vitamin D and sun exposure
Milk-alkali syndrome		High calcium intake increases gastrointestinal absorption and reduces kidney clearance of calcium	Elevated	Low	Normal or low[e]	Low	Discontinue calcium supplement ingestion

Abbreviation: PTH, parathyroid hormone.

[a] Serum calcium is mildly elevated in most patients with primary hyperparathyroidism in developed countries but occasionally presents with more severe elevation.

[b] Severe or symptomatic hypercalcemia requiring immediate treatment should follow Table 2.

[c] Elevated 25-hydroxyvitamin D is consistent with intoxication.

[d] Elevated or inappropriately normal levels consistent with 1,25-dihydroxyvitamin D–mediated processes.

[e] May be high if associated with high dairy intake.

measurement of vitamin A concentrations, and other testing may be appropriate (Figure 1). Measurement of serum phosphate, urinary calcium, and magnesium may help with diagnosis (**Table 1**). Both PTH and PTHrP decrease serum phosphate by reducing kidney sodium-phosphate cotransporter–dependent phosphate reabsorption.[53] In contrast, vitamin D–dependent hypercalcemia is often characterized by elevated serum phosphate due to increased intestinal absorption.[53] Urinary calcium excretion is elevated in most people with malignant hypercalcemia and in many with PHPT.[54] Urinary calcium tends to be low in FHH, in milk-alkali syndrome, or with thiazide use.

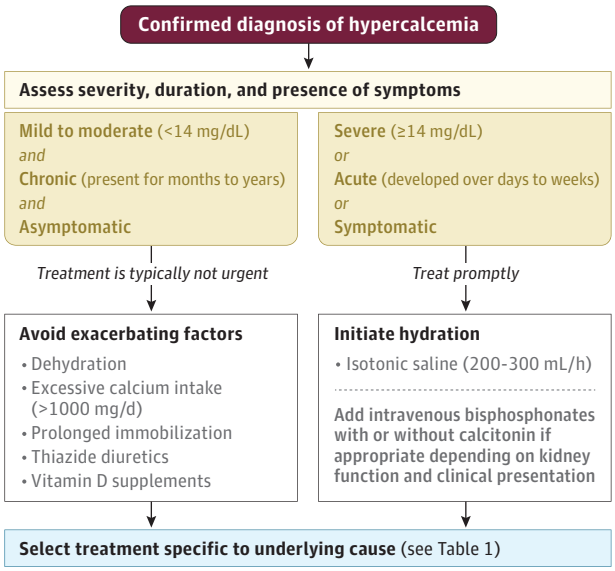
Distinguishing PHPT from FHH is important because FHH is typically managed without surgery. Serum magnesium is high-normal or high in FHH, while urinary calcium excretion is typically low. Fractional excretion of calcium is usually less than 0.01 in FHH, but typically greater than 0.02 in PHPT. However, up to 20% of patients with FHH have fractional excretion of calcium values greater than 0.01. Genetic testing for FHH (*CASR*, *GNA11* [FHH2], and *AP2S1* [FHH3]) and inherited PHPT is appropriate in young patients and those with a family history, fractional excretion of calcium of less than 0.02, multigland disease, parathyroid carcinoma, or features of syndromic PHPT.[43]

Treatment

Management of Mild or Moderate and Asymptomatic Hypercalcemia

Treatment is determined by severity and symptoms (**Figure 2** and

Figure 2. Approach to Treatment of Hypercalcemia


Confirmed diagnosis of hypercalcemia
Assess severity, duration, and presence of symptoms
Mild to moderate (<14 mg/dL)
and
Chronic (present for months to years)
and
Asymptomatic
Severe (≥14 mg/dL)
or
Acute (developed over days to weeks)
or
Symptomatic
Treatment is typically not urgent
Treat promptly
Avoid exacerbating factors
• Dehydration
• Excessive calcium intake (>1000 mg/d)
• Prolonged immobilization
• Thiazide diuretics
• Vitamin D supplements
Initiate hydration
• Isotonic saline (200-300 mL/h)
Add intravenous bisphosphonates with or without calcitonin if appropriate depending on kidney function and clinical presentation
Select treatment specific to underlying cause (see Table 1)

PHPT indicates primary hyperparathyroidism. This diagnostic algorithm has not been validated previously.

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Box 3. Commonly Asked Questions

How Is Primary Hyperparathyroidism Diagnosed?

Primary hyperparathyroidism is diagnosed when there is an elevated serum total (corrected for albumin) or ionized calcium level and a concomitant serum parathyroid hormone (PTH) level that is above normal. PTH levels within the normal range are also consistent with PHPT because hypercalcemia should suppress PTH secretion. For patients with hypercalcemia and PTH levels close to the lower limit of the normal range, other causes of hypercalcemia should be investigated.

What Are the Indications for Parathyroidectomy in Patients With PHPT?

Parathyroidectomy is recommended for patients with classic features of PHPT such as symptoms of hypercalcemia, kidney stones, or osteitis fibrosa cystica. Parathyroidectomy is also recommended for asymptomatic patients with any 1 of the following: (1) serum calcium of greater than 1 mg/dL (0.25 mmol/L) above the upper limit of normal; (2) bone mineral density T score of −2.5 or lower at any site; (3) vertebral fracture on spine imaging; (4) creatinine clearance of less than 60 mL/min/1.73 m^2; (5) nephrocalcinosis or nephrolithiasis by ultrasound or x-ray; (6) urinary calcium excretion of greater than 250 mg/d (>6.2 mmol) for women or greater than 300 mg/d (>7.48 mmol) for men; and (7) age less than 50 years.

How Should Severe Hypercalcemia Be Managed?

Severe hypercalcemia (serum calcium ≥14mg/dL or 3.5 mmol/L) is managed with saline hydration, calcitonin, and intravenous zoledronic acid (5 mg over 15 minutes), which should be administered with or soon after initiation of hydration. If serum creatinine is elevated, consider slower infusion rates (30-60 minutes) or lower doses of zoledronic acid or consider denosumab, which is not cleared by the kidney, instead of zoledronic acid.

Box 3). Patients with mild or moderate hypercalcemia that is asymptomatic do not need immediate treatment. They should avoid exacerbating factors (dehydration, calcium intake >1000 mg/d, immobilization). If feasible, thiazide diuretics should be discontinued. Vitamin D supplements should be discontinued until serum measurements are available. If vitamin D levels are low and hypercalcemia is not likely vitamin D mediated, vitamin D supplements may be resumed. Chronic moderate hypercalcemia that is mildly symptomatic (eg, fatigue) may not require immediate treatment. However, if nausea, vomiting, dehydration, or altered mental status are present, therapy for severe hypercalcemia should be instituted. Definitive management of mild hypercalcemia requires treatment of the underlying cause (Table 1), including discontinuation of contributing medications if clinically indicated.

Most patients with chronic, mild hypercalcemia have PHPT. In the US, most patients with PHPT are "asymptomatic" because they do not manifest any of the classic features of PHPT, namely symptoms of hypercalcemia, nephrolithiasis, or osteitis fibrosa cystica. For such asymptomatic patients, the Fifth International Workshop on the Management of Primary Hyperparathyroidism Guidelines recommend parathyroidectomy for those who meet any 1 of the following criteria[55]: (1) serum calcium of greater than 1.0 mg/dL above the upper normal limit; (2) dual-energy x-ray absorptiometry T score of −2.5 or lower at the spine, hip, or distal 1/3 radius; (3) presence of a vertebral fracture on imaging; (4) creatinine clearance of less than 60 mL/min/1.73 m^2; (5) 24-hour urine calcium excretion of greater than 250 mg (>6.2 mmol) for women and greater than 300 mg (>7.48 mmol) for men; (6) presence of subclinical nephrolithiasis or nephrocalcinosis on imaging; or (7) age less than 50 years. These criteria identify people more likely to develop classic features of PHPT. The American Association of Endocrine Surgeons guidelines include neurocognitive/psychiatric symptoms and cardiovascular disease as criteria for parathyroidectomy. However, evidence is weak for these criteria.[56] Patient preference, availability of surgical expertise, and clinical judgment are important considerations for the decision for parathyroidectomy. Even if no criteria are met, parathyroidectomy remains an option if there are no contraindications to surgery because it is the only cure for PHPT.

Parathyroidectomy should be performed by an experienced parathyroid surgeon. Surgical approaches include minimally invasive parathyroidectomy and bilateral neck exploration. The surgical approach is determined according to local surgical expertise and resources and whether the affected gland(s) can be localized on imaging. In most patients with PHPT, a single adenomatous gland is responsible and can be removed to cure the hyperparathyroidism. In approximately 15% of patients with PHPT, multiple or all 4 glands may be abnormal and more extensive surgery is necessary, ranging from removal of 2 glands to a sub–total parathyroidectomy (3.5 glands). Hypoparathyroidism is rare after parathyroidectomy if these procedures are performed by an expert parathyroid surgeon. In 1 case series (1112 neck explorations) performed by experienced surgeons, transient hypocalcemia occurred in 1.8% of patients and permanent hypoparathyroidism in 0% after parathyroidectomy.[57] Multi-institutional data (n = 6428) suggest that postparathyroidectomy hypocalcemia is present in 2.4% of patients at 180 days, although this may represent transient, not permanent, hypoparathyroidism.[58] Total parathyroidectomy with forearm autotransplantation of parathyroid tissue is no longer recommended due to a high risk of hypoparathyroidism.

Patients who do not meet surgical guidelines for parathyroidectomy can be managed safely without surgery for many years (studies followed patients for 10-15 years). Some patients who meet criteria for parathyroidectomy may be unable to undergo surgery or refuse. In these patients, serum calcium and kidney function should be monitored at least yearly and dual-energy x-ray absorptiometry should be performed annually to biannually.[55] Indications for surgery include the development of criteria 1 through 3 as described above or development of a kidney stone.[55] Bisphosphonates have not been specifically approved for treatment of osteoporosis in PHPT but are often used in patients with osteoporosis who refuse surgery. In an RCT of 44 patients with PHPT randomized to alendronate, 10 mg/d, or placebo, bone mineral density increased 4.9% and 4.0% at the spine and hip, respectively, at 12 months, with no change in the placebo group.[59] Cinacalcet (discussed below) is not indicated for asymptomatic mild to moderate hypercalcemia due to PHPT.

Treatment of Severe or Symptomatic Hypercalcemia

Severe hypercalcemia is life-threatening. Therefore, treatment is often required before the cause is known (**Table 2** and Figure 2). Most patients with severe hypercalcemia are severely dehydrated.

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Table 2. Medical Treatment of Symptomatic Moderate to Severe Symptomatic Hypercalcemia

Agent	Mechanism of action	Adult dose	Adjustment for kidney dysfunction	Onset	Efficacy in hypercalcemia[a]	Potential adverse events
Saline intravenous hydration	Increase glomerular filtration rate, filtered calcium load, increase calcium excretion	Initially 200-300 mL/h, then titrate to urine output	Reduce infusion rate if fluid overload is a concern	Immediate	22%[60]	Volume overload
Loop diuretics[b]	Increase urine calcium excretion	20-40 mg		Hours		Low potassium, worsening kidney function
Calcitonin	Inhibit bone resorption, increase urine calcium	4 IU/kg subcutaneously; maximum, 8 IU/kg	None	4-6 h	30.7%[61]	Allergy, nausea, local skin reactions, flushing, rash, pruritus
Bisphosphonates						
Pamidronate	Inhibit bone resorption	60-90 mg intravenously over 2 h	For mild to moderate kidney dysfunction, common practice is to decrease dose to 30 mg and prolong infusion time (up to 360 min); limited pharmacokinetic data in patients with creatinine clearance <30 mL/min/1.73 m^2	1-2 d	69.7%[62]; 75.8%[63]	Fever, myalgias, fatigue, bone pain, hypocalcemia, hypophosphatemia, uveitis, scleritis, kidney dysfunction
Zoledronic acid	Inhibit bone resorption	4 mg intravenously over 15 min	Consider increasing infusion time to 30-60 min and/or decreasing dose to 2 mg depending on the severity of kidney disease and whether it antedates hypercalcemia	1-2 d	88.4%[62]	Fever, myalgias, fatigue, bone pain, hypocalcemia, hypophosphatemia, uveitis, scleritis, kidney dysfunction
Ibandronate[c]	Inhibit bone resorption	2-6 mg intravenously over 2 h			76.5%[63]	Fever, myalgias, fatigue, bone pain, hypocalcemia, hypophosphatemia, uveitis, scleritis, kidney dysfunction
Denosumab[d]	Inhibit bone resorption	120 mg subcutaneously[e]	FDA labeling does not recommend dose reduction; 0.3 mg/kg or 60 mg subcutaneously is suggested by some experts and publications for bisphosphonate-naive patients in whom bisphosphonates cannot be used due to poor kidney function or allergy	4 d	64% in bisphosphonate-refractory hypercalcemia[64]	Hypocalcemia, hypophosphatemia, rash, infection
Glucocorticoids	Decrease gastrointestinal absorption and 1,25-dihydroxyvitamin D synthesis by mononuclear and lymphoproliferative cells; increase urine calcium excretion	20-40 mg orally	Not applicable	2-5 d	47%[65]	Hyperglycemia, hypertension, myopathy, infection, bone loss/avascular necrosis if chronic
Dialysis	Remove ionized calcium from extracellular fluid			Hours		

Abbreviation: FDA, US Food and Drug Administration.

[a] Refers to calcium response to treatment, variably defined; data derive from different trials with different entry criteria, outcomes, etc, so caution must be exercised in comparing efficacy rates.

[b] Avoid using unless there is a high risk of fluid overload; if required, use only after euvolemia has been achieved.

[c] Ibandronate is not approved by the FDA, but is approved by the European Medicines Agency, for treatment of hypercalcemia.

[d] The FDA-approved dose for bisphosphonate-refractory hypercalcemia is 120 mg; no dose is specifically approved for bisphosphonate-naive patients in whom bisphosphonates cannot be used due to kidney function or a bisphosphonate allergy; may consider a lower dose in these situations, particularly in those with more moderate hypercalcemia (<14 mg/dL).

[e] For hypercalcemia of malignancy, per FDA labeling, administer 120 mg every 4 weeks with additional 120-mg doses on days 8 and 15 of the first month of therapy.

Therefore, initial treatment of severe hypercalcemia includes hydration with saline. Similarly, increased bone resorption is either responsible for or substantially contributes to most etiologies of hypercalcemia, and prompt treatment with intravenous bisphosphonates such as zoledronic acid, pamidronate, and/or calcitonin is usually indicated. The approach should be modified based on clinical factors. Hydration alone might be sufficient when the cause is known and readily reversible (eg, milk-alkali syndrome). In contrast, hydration alone is typically insufficient with hypercalcemia of malignancy. Glucocorticoids may be an initial adjunctive therapy in those with known or highly suspected vitamin D–mediated hypercalcemia and can be used as an additional therapy in refractory

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life-threatening hypercalcemia of any cause. Once acute hypercalcemia is controlled and the cause identified, treatment can be tailored to pathophysiological mechanism (Table 1).

Hydration | Hydration with isotonic saline at a rate of 200 to 300 mL/h should be administered with a goal of attaining urine output of 100 to 150 mL/h. Loop diuretics should be avoided unless there is a high risk of fluid overload, and if required, should be delayed until euvolemia has been achieved.

Bisphosphonates | Intravenous bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption that provide longer-term control of hypercalcemia than saline.[60] Intravenous bisphosphonates should be initiated concomitant with or shortly after hydration is started because these drugs require 24 to 36 hours to lower serum calcium level. One dose of zoledronic acid (4 mg intravenously over 15 minutes) has superior efficacy to pamidronate (90 mg over 2 hours) for treating hypercalcemia of malignancy (serum calcium >12 mg/dL): pooled data from 2 RCTs in patients with hypercalcemia of malignancy (n = 287) demonstrated that 1 dose of 4 mg of zoledronic acid reduced serum calcium to 10.8 mg/dL or lower by day 10 in 88.4% of patients, compared with 86.7% with 8 mg of zoledronic acid and 69.7% with 90 mg of pamidronate.[62] Zoledronic acid achieved reduction in calcium for longer (30 and 40 days for 4-mg and 8-mg doses, respectively, compared with 17 days for pamidronate). Rates of grade 3 or 4 elevations in serum creatinine levels (serum creatinine increase of >3.0-6.0 or >6.0 times baseline value or upper normal limit, respectively, defined according to the Common Terminology Criteria for Adverse Events Version 5) were 5.2%, 2.3%, and 4% for 8 mg of zoledronic acid, 4 mg of zoledronic acid, and pamidronate, respectively. Zoledronic acid, 4 mg, has similar efficacy and lower kidney toxicity than zoledronic acid, 8 mg, and is approved by the US Food and Drug Administration for hypercalcemia. Head-to-head trials of zoledronic acid vs pamidronate for treating hypercalcemia due to other causes are not available. Case reports/case series and small RCTs support their use to treat PHPT, immobilization, hypervitaminosis D, and sarcoidosis.[66-69] For recurrent hypercalcemia, zoledronic acid and pamidronate can be readministered after a minimum of 7 days if severe hypercalcemia persists and more specific treatment cannot be initiated. Intravenous ibandronate, approved for treatment of hypercalcemia in Europe but not the US, has comparable efficacy to pamidronate (Table 2).[70,71]

Intravenous bisphosphonates have been associated with collapsing focal segmental glomerulosclerosis and acute tubular necrosis and rarely may result in kidney failure and dialysis. Preexisting kidney disease may increase susceptibility. It is important to recognize that hypercalcemia may increase creatinine due to associated dehydration and that both hypercalcemia and increased creatinine may improve with bisphosphonate therapy. Ensuring adequate hydration with saline, avoiding other nephrotoxins, and using a lower dose and/or slower infusion rate of bisphosphonate (Table 2) may minimize risk.

Clinicians often prefer pamidronate over zoledronic acid in patients with chronic kidney disease due to a perceived lower risk of nephrotoxicity.[62] However, in a recent retrospective study of 113 adults with hypercalcemia and creatinine clearance of less than 60 mL/min/1.73 m^2, there was no difference in the rate of creatinine elevation between patients who received zoledronic acid (3-4 mg over 15-60 minutes) and those receiving pamidronate (15-90 mg over 120-360 minutes). Rates of elevated creatinine were 24.1% and 27.3%, respectively. Grade 3 or grade 4 serum creatinine elevations were more common in those with pretreatment creatinine clearance of less than 30 mL/min/1.73 m^2 than in those with 30 mL/min/1.73 m^2 or greater. However, grade 3 or 4 creatinine elevations occurred in 10.9% of patients treated with pamidronate vs 1.7% treated with zoledronic acid. Patients receiving pamidronate were more likely to have baseline creatinine clearance of less than 30 mL/min/1.73 m^2. These retrospective data suggested that pamidronate does not have a lower risk of nephrotoxicity.

Combination Therapy With Calcitonin | Calcitonin inhibits bone resorption and increases urine calcium excretion. Because the onset of action for calcitonin is hours while that of bisphosphonates is 1 to 2 days, calcitonin is useful for rapidly lowering calcium in patients with severe hypercalcemia. Calcitonin can be started simultaneously with hydration and bisphosphonates (Table 2) and discontinued after 48 hours, when tachyphylaxis develops. In a retrospective study of moderate or severe hypercalcemia, calcitonin plus a bisphosphonate (n = 46) was associated with greater lowering of calcium after 48 hours of treatment compared with bisphosphonate alone (n = 94).[72] There were no differences in corrected calcium levels at 24 to 72 hours, rates of normocalcemia, or hospital length of stay. Mean baseline calcium was higher in the combination group (13.9 mg/dL vs 12. 6 mg/dL). Although the authors suggested that calcitonin increases expense without substantial clinical benefit,[72] the retrospective design precluded any definitive conclusion. If available, calcitonin may have utility in patients with life-threatening hypercalcemia in whom it is important to lower calcium as quickly as possible or when bisphosphonates are contraindicated.

Denosumab | Data regarding denosumab to treat acute hypercalcemia are limited. Two small case series (total n = 14) reported that denosumab decreased serum calcium in patients presenting with severe hypercalcemia related to parathyroid crisis/severe hyperparathyroidism who could not undergo urgent parathyroidectomy.[73,74] In 2015, the US Food and Drug Administration approved denosumab, 120 mg subcutaneously, for treating hypercalcemia of malignancy that is refractory to bisphosphonates. In an open-label, single-group study of 33 patients with advanced cancer and persistent hypercalcemia after bisphosphonate treatment, 63.6% responded (serum calcium <11.5 mg/dL) within 10 days.[64] Denosumab, 120 mg, was more effective than zoledronic acid, 4 mg intravenously, every 4 weeks for preventing hypercalcemia[75]: 1026 women with metastatic breast cancer randomized to denosumab had fewer hypercalcemia events compared with those randomized to zoledronic acid (28 vs 58 events; rate ratio, 0.48; $P = .04$).[75] Denosumab is also effective for parathyroid cancer–related refractory hypercalcemia.[76]

Although denosumab may be particularly appropriate for those with severe kidney dysfunction because it is not cleared by the kidney, there are no data to indicate the level of chronic kidney disease that renders denosumab preferable to intravenous bisphosphonates to treat acute hypercalcemia. Data are primarily

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from studies in patients with malignancy who are receiving chronic denosumab treatment. A meta-analysis of 4 RCTs involving 7201 patients compared the safety of long-term denosumab with zoledronic acid in patients with skeletal metastases or myeloma. Denosumab was associated with a lower risk of kidney toxicity (9.2% vs 13.0%; risk ratio, 0.69; 95% CI, 0.54-0.87; $P < .01$) but higher risk of hypocalcemia (9.9% vs 5.8%; risk ratio, 1.78; 95% CI, 1.33-2.38; $P < .01$).[77] Vitamin D deficiency and kidney dysfunction increase risk of denosumab-related hypocalcemia. Denosumab, 60 mg, or a weight-based dose (0.3 mg/kg), has been proposed by some experts for bisphosphonate-naive patients with moderate hypercalcemia (<14 mg/dL) and/or chronic kidney disease.[78]

Glucocorticoids and Ketoconazole | Glucocorticoids inhibit gastrointestinal calcium absorption, increase urinary calcium excretion, and inhibit 1α-hydroxylase activity. They are indicated as primary treatment for vitamin D intoxication, noninfectious granulomatous disorders, and some lymphomas in which hypercalcemia is due to intestinal calcium hyperabsorption. Prednisone dosages of 20 mg/d to 40 mg/d, sometimes higher, are usually required. Ketoconazole, an imidazole antifungal, inhibits calcitriol production in sarcoidosis, tuberculosis, silicone-related granulomatous disease, and people with *CYP24A1* variants.[79-82] Ketoconazole is an alternative to glucocorticoids or may be used in conjunction with lower doses of glucocorticoids. Patients with increased calcium absorption should limit dietary calcium and vitamin D, avoid sun, and maintain hydration. Seasonal exacerbation of hypercalcemia has been described in patients with sarcoid and *CYP24A1* variants.[83,84] In patients with hypercalcemia related to solid tumors, bisphosphonates and/or denosumab were less effective if calcitriol was elevated.[85] Glucocorticoids or ketoconazole might be helpful.

Kidney Replacement Therapy | Hemodialysis with a low- or no-calcium dialysate is generally reserved for severe refractory hypercalcemia, serum calcium levels above 18 to 20 mg/dL with neurological symptoms, and patients with heart failure or kidney disease who cannot tolerate hydration.

Cinacalcet | Cinacalcet, a type 2 calcimimetic that increases CaSR sensitivity, is approved for treating hypercalcemia due to parathyroid cancer or severe PHPT when parathyroidectomy is not possible. There is limited evidence regarding treating acute hypercalcemia related to parathyroid crisis, but cinacalcet can be added after hypercalcemia is controlled by other measures or in outpatients with worsening parathyroid-related chronic hypercalcemia (Table 1).[86] Cinacalcet temporarily improved serum calcium in a few cases of hypercalcemia of malignancy.[87,88]

Prognosis

Although treatment lowers serum calcium and improves symptoms in most patients, long-term prognosis depends on the cause of hypercalcemia. In a recent study, in-hospital mortality was 17% in hospitalized patients with hypercalcemia and higher calcium levels were associated with increased mortality.[89] Most patients with hypercalcemia due to malignancy die within 1 year.[90] In contrast, the prognosis for asymptomatic PHPT is excellent with or without surgery. Parathyroidectomy is curative in 95% or greater when performed by experienced surgeons.[91,92] Randomized clinical trials and observational data indicate that parathyroidectomy is associated with normalization of serum calcium and increases in bone mineral density.[93-95] Five years after randomization to parathyroidectomy or observation, spine Z score increased by 0.08 with observation and 0.35 with parathyroidectomy.[95] With medical monitoring, calcium as well as bone mineral density typically remain stable over time. However, after 10 to 15 years, almost 40% of patients developed 1 or more criteria for surgery.[96] Some studies indicated increased mortality in severe PHPT, but the effect of asymptomatic PHPT on mortality and benefit of parathyroidectomy are controversial. An observational study of 16 374 patients with PHPT and 163 740 control patients indicated that those with PHPT had a higher risk of death (51.83 vs 30.95 per 1000 person-years) and parathyroidectomy reduced risk (hazard ratio, 0.59).[97] A smaller RCT of 191 patients reported no benefit of parathyroidectomy on mortality compared with observation at 10-year follow-up (25.3% vs 20.8%).[98]

Limitations

This review has several limitations. First, the quality of included articles was not evaluated. Second, many of the identified studies were not RCTs. Third, some recommendations are based on guideline statements (which may be expert opinion) or observational data. Fourth, the literature search may have missed some relevant publications.

Conclusions

Mild hypercalcemia is typically asymptomatic, while severe hypercalcemia is associated with nausea, vomiting, dehydration, confusion, somnolence, and coma. Asymptomatic hypercalcemia due to primary hyperparathyroidism is managed with parathyroidectomy or observation with monitoring, while severe hypercalcemia is typically treated with hydration and intravenous bisphosphonates.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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